THE LUNG CANCER PROBLEM

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Mr. Chairman, it is unfortunate that the role of cigarette smoking in the etiology of cancer of the lung has been pursued with such vigor, and almost evangelical fervor, that there is a widespread impression that the smoking of cigarettes is the only agent incident to the cause of lung cancer. Even laymen have joined in this chorus of attack until fright has taken the place of calm, scientific investigation of the clinical problem, and careful, basic research; this has led to a chaotic situation in which physicians have staunchly taken sides, and closed their senses and minds to careful appraisal of all the evidence presented by equally talented trained scientists and clinicians until it is unpopular with one group to differ with the other. To paraphrase a remark made by Sir Winston Churchill, when an attack is launched for a predetermined idea, one who differs, becomes a reactionary. I do not want to give the idea there is any personal aggressiveness among physicians, for one of my oldest and affectionate friends is one who declines to see both sides of our problem. The truth is that differences of interpretation calmly appraised, is the only way the true facts will become known regarding this problem of cancer of the lung. My study of lung cancer, as an independent internist and diagnostician has convinced me to agree with Dr. Joseph Berkson, Mayo Clinic, that there is no proof of any proved causal relationship between the smoking of cigarettes and lung cancer, when he states in an article in Cancer Journal, "Without false modesty, and quite frankly, I do not know the cause of cancer. Morevoer, I am going to say without slight fear of contradiction, that no one else does either." Other members of the Mayo Clinic have said, "Perceptive minds have noted that if one wishes to know what a scientist believes, one should not attend

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to what he says, but to what investigations he projects." There is no doubt that subjective bias plays an important part in the writing of research papers, as well as in the collection of data, and there is no double blind test to exclude it, as stated by Passey. Nowhere has it been shown that the heavy cigarette smoker is stricken with lung cancer earlier than the light- or non-smoker. It is interesting to note, as again confirmed by Passey, that in the United Kingdom, males smoke fewer cigarettes but have more than three times as much lung cancer as males in Australia. It has been stated by a well known thoracic surgeon, "There are still a few physicians, although the number is decreasing, who deny a causal relationship between smoking and cancer, but these, without exception, are either employees of the tobacco industry or addicted themselves." Sir, I present myself as one exception, as I have never smoked cigarettes, and I am not an employee of the tobacco industry. Let us calmly, without prejudice, consider this problem of the etiology of lung cancer.

My thesis is that we do not really know any one factor, or element, to be ~~the~~ a cause of cancer of the lung. We ~~know that~~ feel that probably more than one agent is operative, perhaps many conditions, both within our bodies, and our environment, are operating. It is unscientific to state, unequivocally, that the smoking of cigarettes is ~~the~~ only factor involved when ~~the~~ evidence ~~against such an assumption~~ to this effect is lacking. Hammond and Machle, discussing the environmental and occupational factors relative to lung cancer, state: "At the present state of our knowledge of the nature of normal and neoplastic growth, it is unlikely that we will soon acquire any very direct evidence of the exact nature and mode of action of many specific carcinogenic agents that may be operating to produce lung cancer in man, or of factors that may increase susceptibility to this disease. Absolutely certain proof that a specific agent causes lung cancer in man could only be obtained by experimenting with human beings; such experimentation is not feasible." Rusch and Berenblum have pointed out that cancer, experimentally induced by chemical agents, is a

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process involving at least two stages, initiation and promotion. Loutit, in a selected abstract, published by the American Cancer Society, is of the opinion that cancer is a normal process of aging, and the mystery is not so much why cancer occurs, but how normally it is so long delayed. Furthermore, it is his opinion, based upon histological evidence, that the cancer cell is undoubtedly a changed form from the normal cell, and that these changes must be a feature of physiological environment. He states that a confounding of nucleic acid metabolism may be a common factor in induction of the primary cancerous change, whether this initiation be a single or a multifactorial process, the establishment of a cancer seems to be dependent on more than one element; the promotion of growth of this primary factor may be facilitated in environment by physical, chemical, and immunological factors.

It is obvious it is not possible for me to discuss with you all the intimate details of the basic and clinical research dealing with the etiology of lung cancer. A great deal of the mass of material is not truly factional because you will not find in the entire literature a definite answer that one agent is the only cause of lung cancer, on the other hand, only opinions are given, such as "casually related," "leads to the judgement," "the evidence on the relationship supports the belief," "an association exists," "in referring to cancer of the urinary bladder in the male," "available data suggest an association between cigarette smoking and bladder cancer in the male." Before we begin to solve this vast problem, we must operate in areas of suspicion and possibility. Therefore, everything depends on the mental processes of the individual observer, which may be entirely different. In most situations any causal role for a suspected agent, like cigarette smoking, is further complicated by difficulties in evaluating the role of that suspected agent and carcinogen or co-carcinogen. The question is was the suspected agent an initiatory one, producing changes in the bronchial mucosa, and then later carcinoma

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is promoted by another agent, such as polluted air, virus infection, and chemical irritation. There is no such thing as unpolluted air, and people are daily subjected to a chemical environment like nothing mankind has experienced before, both in kind and extent of his exposures. There is no doubt that there is a tremendous amount of exposure to carcinogens in the atmosphere, particularly in urban areas, but, also, to a lesser extent in rural areas. Auerbach and Stout have stated: "The word precancerous does not signify the lesion inevitably leads to invasive cancer, but only that it may do so." They were referring to changes in the tracheobronchial tree under the influence of inhaled carcinogens (cigarette smoke), and indicated the danger of a false diagnosis, specifying the lesion may be considered occult only when the lining of the tracheobronchial tree is entirely replaced by anaplastic cells entirely comparable to the cells found in invasive carcinoma.

When we consider air pollutants, we must remember that in susceptible individuals, physiological alterations following exposure to irritants are accompanied by histologically demonstratable changes in the respiratory epithelium. This change is primarily an increase in the number and activity of goblet cells, which progresses until there is almost complete replacement of the normal epithelium by an overgrowth of mucus-producing cells; the epithelium becomes covered by pools of mucus, and finally, these mucus lakes empty into the lumen of the tracheobronchial tree, with complete desquamation of the epithelium down to the basal cells. This is a primary, or initiatory step, and represents a sequence in which noncarcinogenic agents appear to facilitate biological activity of compounds capable of inducing cancer in the respiratory tract. Expressed in other words, it is the pattern of initiation, not necessarily followed by the promotion of cancer, but is fundamentally necessary for the development of invasive cancer. In the meantime, the lungs are subjected to many irritants, in fact too many to authoritatively single out one culprit.

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The most ubiquitous carcinogenic agents detected in the atmosphere belong to a group of polycyclic aromatic hydrocarbons (PAH) present in the atmosphere. Goulden and Tipler (1949) identified benzo[a]pyrene (BaP) in domestic soot, and the characterization of benzpyrene in Great Britain by Waller (1952) of the presence of carcinogenic benzpyrene has been confirmed in urban polluted atmospheres. Sawicki et al have analyzed the concentration of benzpyrene in selected urban and nonurban areas in eight states in the United States, all of which showed the carcinogen benzpyrene in both urban and nonurban air, the urban areas showing a greater amount than the nonurban. It was interesting, and suggestive, to note that of the eight, Pennsylvania, Missouri, and Indiana - more populous states - had a greater amount of benzpyrene in the air than the other five states included in his study. The minute amounts of benzpyrene and other PAH found in cigarette smoke are evident insignificance when compared to the amounts to which all of us are subjected by the way we breathe.

There is a definite role for environmental factors in the pathogenesis of lung cancer as has been demonstrated since Härting and Hesse (1879) reported lung cancer in radioactive ore miners in Schnecberg as the first instance in which atmospheric environment was the apparent source of a pulmonary carcinogenic agent. Since that time, increased mortality from cancers of the respiratory tract has been shown to be associated with a number of occupational agents, among which we may briefly mention, fluospar miners, chromate workers, employees in nickel refineries, and workers with asbestos. It has also been recognized that persons exposed occupationally to gases and fumes from the combustion and distillation of coal in coking operations and gas generating plants are exposed to potential carcinogenic agents.

There is no doubt that there is considerable occupational exposure to carcinogens. For instance, thousands of tons of lead are mined annually to be distributed as dusts from paints, the use of gasoline and diesel oils has resulted in a significant source of carcinogens in some communities. Falk et al mentioned a secondary source of PAH is the carbon black incorporated in the manufacture of

He has noted that 75% of the Schneeberg miners developed lung cancer, and that the carcinogenic effect of chromate, nickel, etc. is supported by positive findings in animal experimentations. In contrast, only a

fraction of 17 of samples got lung cancer, and all animal inhalation experiments have been negative.

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rubber tires, which due to the wear and tear incidental to general use, result in the dissemination of dusts from which carcinogenic PAH may be eluted when the engines operate inefficiently. Survival studies on both crystalline PAH and those absorbed on soot demonstrate that their recovery rate is consistent with their persistence in the atmosphere for sufficient periods to be respired by exposed people (Falk et al 1956). The rate of disappearance of the carcinogen is lower in the strong oxidizing air, such as occurs in Los Angeles smog (Haagen-Smit, 1952). It has been concluded by Stocks and Campbell (1955), "The concentration of smoke and of 3:4-benzpyrene, other polycyclic hydrocarbons, and sulphur dioxide in the air, rises with increasing urbanization, the benzpyrene figure in Liverpool being 8 to 11 times as great as in the rural localities examined, a ratio which corresponds with the estimated mortality ratio among nonsmokers living in these areas." Stokes, (1952), in another study in Great Britain, aimed at evaluating the relation of atmospheric pollution in urban and rural communities with mortality rates from cancer, concluded that lung cancer mortality is strongly correlated with the smoke density in the atmosphere in 26 areas of Northern England and Wales, 45 districts in Lancastershire, and 30 county boroughs. Herbich and Neubold (1954) demonstrated the same findings as Stokes in Austria, with the highest rates in Vienna, the lowest rate in rural Austria. Similar consistent and parallel observations authenticate a role for the urban factor as one cause of lung cancer in man.

Raeburn and Spencer (1953) were among the earliest scientists to draw attention to the causal relationship between chronic bronchitis and the increased liability to the development of lung cancer. This observation has been corroborated by others. Pulmonary tumors have been found adjacent to foci of scarring and long-term chronic inflammations of the lung. It has been found in a national survey, carried out by the Respiratory Study Group of the College of General Practitioners in Great Britain, that chronic bronchitis in Great Britain follows an epidemiolo-

gical pattern analogous to that of lung cancer. Quoting from the National Survey, (1961), the evidence supported the following conclusions:

"1. The significant differences in smoking habits found between town and country are not enough to explain the urban-rural gradient in male morbidity.

"2. Small differences in smoking habits have no material effect upon the social-class gradient in chronic bronchitis prevalence.

"3. Sex differences in prevalence rates, however, may be largely explained by differences in cigarette consumption, but the lower sex-ratio found in random samples of practice populations compared with that in - for example, death rates and admission rates in hospitals - strongly suggest the lesser severity of chronic bronchitis in women."

There is a question whether the increase in lung cancer has been real or relative, and a number of investigators of eminence have advocated caution in wholly accepting that the increase is real. Willis (1961), on the basis of study of autopsy records from 1903 to 1960, concluded that, "A large part of the great increase in registered deaths from lung cancer, which has occurred in this century, is certainly due to better diagnosis and to a greater clinical awareness of the disease. Whether or not there has also been a real increase in its frequency, it is impossible to be sure." Studies by Gilliam (1955) emphasized the possible contribution of erroneous diagnoses, particularly that of tuberculosis, to the increase in lung cancer. Rigdon et al (1955) and Rigdon and Kerchoff (1961) concluded that a major portion of the increase in lung cancer in Texas may be spurious. Dormanns (1955) in Germany similarly questioned the extent of the real increase in lung cancer, and concluded, "According to my lights, the increase in cancer incidence may be attributed in all probability and primarily to a numerical factor as such is reflected in the changes in the age group distribution of the population."

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The problem of our present-day "population explosion" must be considered when we evaluate the mortality rate of lung cancer on a definite numerical basis. It is difficult to evaluate such statistics percentagewise. The population estimates of the Population Reference Bureau in Washington, D. C. for 1964 and 1980 are at present rates of growth (in millions) for North America, 211 for 1964 and 267 for 1980, and for the world totals 3283 for 1964 and 4274 for 1980.

Scientific investigators, who are really trying to solve this problem, must realize the cause or causes of lung cancer will never be solved except by scientists, consecretated to the truth, unprejudiced, and unbiased. We should get down to the business of really solving the etiology of not only lung cancer but of cancer as a whole. It is my opinion from a basic etiological standpoint that when we have solved the facets of fundamental cancer research, we may be able to begin to unravel the true causal or etiological factors of cancer in general, as well as localized cancer. It is my personal opinion there is a definite relationship between the basic, causal factors of lung cancer and cancer elsewhere in the body, and unless we approach the solution of this major problem from that viewpoint, the ultimate solution of the ~~etiology~~ causation of lung cancer will be greatly delayed. We must not further delay that solution by emotionally committing ourselves to popular concepts such as cigarettes, and thereby deter objective research that will lead to a true solution to the problem.

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